ORIGINAL ARTICLE INFECTIOUS DISEASES

Characteristics of prosthetic joint infections due to *Enterococcus* sp. and predictors of failure: a multi-national study

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Abstract

The objective of this study was to review the characteristics and outcome of prosthetic joint infections (PJI) due to *Enterococcus* sp. collected in 18 hospitals from six European countries. Patients with a PJI due to *Enterococcus* sp. diagnosed between January 1999 and July 2012 were retrospectively reviewed. Relevant information about demographics, comorbidity, clinical characteristics, microbiological data, surgical treatment and outcome was registered. Univariable and multivariable analyses were performed. A total of 203 patients met the inclusion criteria. The mean (SD) was 70.4 (13.6) years. In 59 patients the infection was diagnosed within the first 30 days (29.1%) from arthroplasty, in 44 (21.7%) between 31 and 90 days, in 54 (26.6%) between 91 days and 2 years and in 43 (21%) after 2 years. *Enterococcus faecalis* was isolated in 176 cases (89%). In 107 (54%) patients the infection was polymicrobial. Any comorbidity (OR 2.53, 95% CI 1.18–5.40, p 0.01), and fever (OR 2.65, 95% CI 1.23–5.69, p 0.01) were independently associated with failure. The only factor associated with remission was infections diagnosed later than 2 years (OR 0.25, 95% CI 0.09–0.71, p 0.009). In conclusion, prosthetic joint infections due to *Enterococcus* sp. were diagnosed within the first 2 years from arthroplasty in >70% of the patients, almost 50% had at least one comorbidity and infections were frequently polymicrobial (54%). The global failure rate was 44% and patients with comorbidities, fever, and diagnosed within the first 2 years from arthroplasty had a poor prognosis.

Keywords: Debridement, *Enterococcus faecalis*, *Enterococcus faecium*, one-stage exchange, outcome, prosthetic joint infection, two-stage exchange
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Introduction

Prosthetic joint infection (PJI) is a severe complication that occurs in 0.5–3% of arthroplasties [1–3] and staphylococci are the most frequently isolated microorganisms [4]. Coagulase-negative staphylococci account for 30–41% and *Staphylococcus aureus* for 12–39%. Gram-negative organisms are less common than Gram-positive, causing around 10% of cases [5]. Among Gram-positive bacteria, *Enterococcus* sp. account for 3–10% [6–8]; however, the isolation of enterococci has been associated with a worse outcome [9,10] probably due to the tolerance of enterococci to different classes of antibiotics. The largest case series was published by El Helou *et al.* [11] where they described 50 cases treated in one institution over 30 years; however, polymicrobial infections were excluded from the analysis and recent data suggest that PJI are frequently polymicrobial—probably due to improvements in sampling and microbiological methods.

The objective of this study was to review the characteristics and outcomes of monomicrobial or polymicrobial PJI due to *Enterococcus* sp. diagnosed and treated in 18 hospitals from six European countries.

Patients and Methods

Setting and patients

Patients with a PJI due to *Enterococcus* sp. diagnosed between January 1999 and July 2012 from 18 hospitals in six European countries (France, Germany, Hungary, Italy, Slovenia and Spain) were retrospectively reviewed. Relevant information about demographics (age and gender), comorbidity (having or not having one of the following entities: coronary disease, diabetes mellitus, malignancy, liver cirrhosis, chronic renal failure or chronic obstructive pulmonary disease), site of implant, type of implant (cemented or non-cemented), age of prosthesis, clinical manifestations (fever and wound drainage), leucocyte count and value of C-reactive protein at the moment of admission for infection, surgical treatment (debridement with retention of the prosthesis, one-step exchange or two-step exchange), isolated microorganisms, antibiotic treatment directed to enterococci, duration of the total antibiotic therapy, and outcome were recorded. Diagnosis of PJI was based upon clinical symptoms and signs (such as joint pain, redness, fever, wound drainage, presence of a sinus tract or purulence, and other inflammatory signs) and isolation of enterococci in at least two deep samples. PJI were divided according to the age of implant at the moment of infection diagnosis into ≤30, 31–90, 91 days to <2 years and >2 years. Information was introduced in a database specially designed for the study. Two co-authors (A.S. and E.T.) reviewed all cases and contacted collaborating centres to clarify controversies.

Outcome and follow up

After being discharged, patients were followed up according to the protocol of each participating centre. Follow-up period was calculated from surgery due to infection: debridement, one-stage exchange or from the second stage in patients who underwent a two-stage exchange. Among patients in remission, only those with at least 1 year of follow up were included in the outcome analysis. Outcome was considered as failure when inflammatory signs remained or re-appeared during or after completing antibiotic treatment and/or the patient needed an unplanned surgery to control the infection. Death-related to infection and need for suppressive antimicrobial therapy were also considered as failures.

Statistical analysis

Variables were express as mean (SD), median (interquartile range) or percentage. Continuous variables were compared by Student's *t*-test and the following variables were also categorized: age (≤70 or >70 years), age of implant (≤30, 31–90 days, 91 days to 2 years or >2 years from arthroplasty), leucocyte count (≤10 000 or >10 000 cells/mm^3), C-reactive protein (<5, 5–12 and >12 mg/dL) at the moment of admission for infection. Categorical variables were compared by the chi-square test or Fisher's exact test when necessary. The Kaplan–Meier survival method was used to estimate the cumulative probability of remission. Variables significantly associated with failure in the univariable analysis were included in a forward logistic regression model to identify independent variables associated with failure. Statistical significance was defined as a two-tailed p-value <0.05. The analysis was performed using SPSS, version 20.0 (SPSS, Inc., Chicago, IL, USA).

Results

Eighteen European centres from six different countries participated in the study. A total of 203 patients with a PJI due to *Enterococcus* sp. met the inclusion criteria. The mean (SD) age of the cohort was 70.4 (13.6) years, and 75 were male (40%). In 128 cases (63%) infection was on a hip prosthesis, in 69 (34%) on a knee prosthesis and in six (3%) on other joints (shoulder or elbow). The most frequent *Enterococcus* sp. was *Enterococcus faecalis*, which was isolated in 176 cases (89%) while *Enterococcus faecium* was found in 19 cases

(9%) and both in three cases (2%). In five cases, the species was not provided. In 107 (54%) patients the infection was polymicrobial and the co-pathogens were coagulase-negative staphylococci (37 cases, 19%), *S. aureus* (24 cases, 12%), *Escherichia coli* (13 cases, 7%), *Pseudomonas aeruginosa* (14 cases, 7%), *Enterobacter cloacae* (four cases, 2%) and other microorganisms (15 cases, 7%). The median (interquartile range) duration of antibiotic treatment was 84 (53–147) days. Debridement, antibiotics and implant retention was performed in 102 (53%) cases, one-stage exchange in 29 (15%) and two-stage exchange in 63 (32%). In nine cases the surgical treatment was not provided.

Those patients in remission but with <1 year of follow up were not considered for the outcome analysis. Therefore, 178 patients were included in the final analysis. After a median (interquartile range) post-surgical follow-up period of 722 (168–1529) days for patients with or without failure, 100 patients (56%) were considered to be in remission and 78 (44%) were considered as failures. Baseline characteristics, surgical management and data according to the outcome are shown in Table 1. Fig. 1 shows the cumulative probability of remission at 2 years of follow up (failures identified later than 2 years are not included in the graph) according to the type of *Enterococcus* sp. (log rank-test, p 0.002).

Infections diagnosed later than 2 years from arthroplasty were associated with a higher remission rate (83%) than those diagnosed ≤30 days (43%), between 31 and 90 days (44%) or between 91 days and 2 years (63%) (p <0.001). Fig. 2 shows the cumulative probability of remission at 2 years of follow up (failures identified later than 2 years are not included in the graph) according to the time from arthroplasty. Implant removal was associated with a higher remission rate; however, the analysis of surgical management (retention or exchanging the implant) according to the age of implant at the moment of infection diagnosis showed that removing the implant was associated with a better prognosis only in those patients with a very late (>2 years from arthroplasty) infection (92% versus 50%, p 0.020; Table 2). In particular, one-stage exchange had a higher success rate (77.3%) than two-stage exchange (57.4%) or debridement (46.8%). The univariable analysis of monomicrobial infections identified the same variables associated with the outcome, and the results in monomicrobial infections according to the age of implant and surgical treatment were similar to those in polymicrobial infections.

Regarding antibiotic treatment, the results for the antibiotic administered for treating enterococci were analysed in infections that occurred ≤30 days from arthroplasty and those diagnosed >30 days after arthroplasty. Only the administration of rifampin, in combination with other antibiotics in early infections was associated with a lower rate of failure than other alternatives (Table 3).

A multivariate analysis using variables significantly associated with the outcome in the univariate analysis was performed. Variables included were having or not having comorbidity, age of prosthesis at the moment of infection diagnosis (>2 years versus others), polymicrobial infection, type of *Enterococcus* sp. (*E. faecalis* versus *E. faecium*), fever, and type of surgical

TABLE 1. Baseline characteristics according to the outcome

Characteristics	Remission *n* = 100	Failure *n* = 78	p value
Mean age (SD) years	71.3 (12.5)	68.1 (15.3)	0.13
Age > 70 years	67 (67.0)	45 (57.7)	0.20
Female	61 (61.0)	49 (62.8)	0.80
Comorbidities[a]			
No comorbidities	48 (52.7)	19 (31.1)	0.009
Diabetes mellitus	19 (20.9)	16 (26.2)	0.44
Coronary disease	15 (23.4)	12 (22.6)	0.92
Chronic renal failure	10 (11.5)	12 (19.7)	0.17
Liver cirrhosis	4 (4.4)	8 (13.1)	0.06
Chronic obstructive pulmonary diseases	7 (10.9)	4 (7.5)	0.75
Malignancy	12 (13.3)	5 (8.2)	0.33
Type of arthroplasty			
Hip	57 (57.6)	55 (70.5)	0.17[g]
Knee	40 (40.4)	21 (26.9)	
Other	3 (3.0)	2 (2.6)	
Type of cement[a]			
Non-cemented	21 (22.8)	13 (21.7)	0.38[h]
Cemented without ATB	69 (75.0)	43 (71.7)	
Cemented with ATB	2 (2.2)	4 (6.7)	
Median (IQR) age of prosthesis in days	148 (32–904)	42 (15–124)	0.007
Age of implant at the moment of diagnosis[b]			
<30 days	23 (23.2)	31 (40.3)	<0.001[i]
30–90 days	19 (19.2)	24 (31.2)	
91 days to 2 years	27 (27.3)	16 (20.8)	
>2 years	30 (30.3)	6 (7.8)	
Wound drainage	54 (60.7)	38 (61.3)	0.94
Fever	28 (28.9)	37 (48.7)	0.008
Mean (SD) leucocyte count (cell/mm^3)[c]	7717 (3375)	10 098 (4102)	0.001
Leucocyte count > 10 000 (cell/mm^3)[c]	13 (21.3)	23 (44.2)	0.009
Mean (SD) C-reactive protein[d]	5.5 (5.1)	7.9 (6.4)	0.02
C-reactive protein			
<5 mg/dL	46 (59.7)	23 (45.1)	0.06
5–12 mg/dL	21 (27.3)	16 (31.4)	
>12 mg/dL	10 (13.0)	12 (23.5)	
Antibiotic before surgery	31 (43.1)	25 (36.8)	0.45
Polymicrobial infection	48 (48)	51 (65)	0.04
Enterococcus sp.[e]			
E. faecalis	89 (92.7)	64 (82.1)	0.04[j]
E. faecium	5 (5.2)	13 (16.7)	
E. faecalis + *E. faecium*	2 (2.1)	1 (1.3)	
Type of surgery[f]			
Debridement	44 (47.8)	50 (64.1)	0.17[k]
One-step exchange	17 (18.5)	5 (6.4)	
Two-step exchange	31 (33.7)	23 (29.5)	
Management of implant			
Retention	44 (47.8)	50 (64.1)	0.03
Exchange (one or two stages)	48 (52.2)	28 (35.9)	
Median (IQR) days of ATB treatment	90 (60–180)	90 (45–148)	0.94

Abbreviations: ATB, antibiotic; IQR, interquartile range.
[a]This variable was evaluated in 152 patients.
[b]This variable was evaluated in 176 patients.
[c]This variable was evaluated in 113 patients (61 in remission and 52 in failure group).
[d]This variable was evaluated in 128 patients.
[e]The species was not provided in four cases.
[f]This variable was evaluated in 170 patients.
[g]Comparison between hip and knee prosthetic joint infection.
[h]Comparison between non-cemented and cemented.
[i]Comparison between >2 years and others.
[j]Comparison between *E. faecalis* and *E. faecium*.
[k]Comparison between one-stage and two-stage exchange.

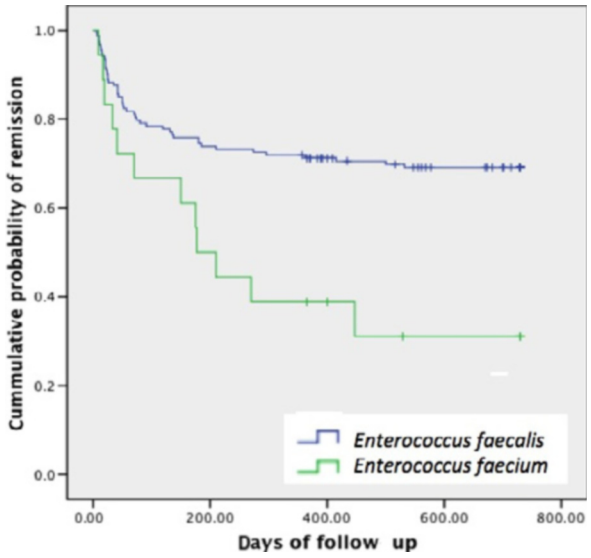

FIG. 1. Cumulative probability of remission at 2 years follow up according to the *Enterococcus* sp. (log-rank test p 0.002).

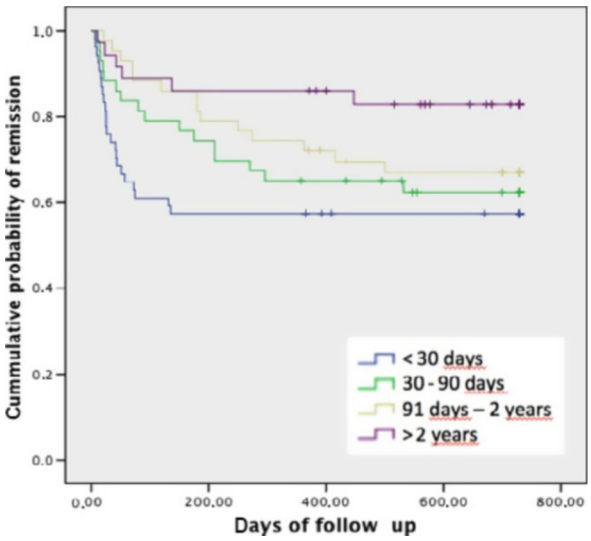

FIG. 2. Cumulative probability of remission at 2 years follow up according to the time from arthroplasty (log-Rank test p 0.044).

treatment (debridement versus exchange). Leucocyte count and C-reactive protein were not included because the number of patients with this information was limited. The final model identified, as risk factors for failure, the presence of any comorbidity (OR 2.53, 95% CI 1.18–5.40, p 0.01), and fever (OR 2.65, 95% CI 1.23–5.69, p 0.01). The only factor associated with remission was infection diagnosed later than 2 years (OR 0.25, 95% CI 0.09–0.71, p 0.009).

TABLE 2. Outcome according to the type of surgical management and type of infection

Age of implant at the moment of infection	Surgery	Remission (%)	Failure (%)	p value
≤30 days	Debridement	20 (41.6)	28 (58.4)	1
	Exchange	2 (40)	3 (60)	
31–90 days	Debridement	12 (46.2)	14 (53.8)	0.58
	Exchange	6 (37.5)	10 (62.5)	
91 days to 2 years	Debridement	8 (66.7)	4 (33.3)	0.72
	Exchange	16 (57.1)	12 (42.9)	
>2 years	Debridement	4 (50.0)	4 (50.0)	0.02
	Exchange	23 (92.0)	2 (8.0)	

TABLE 3. Outcome of different antibiotics used against enterococci according to the age of implant at the time of infection

Age of implant at the moment of infection	Type of antibiotic	Remission (%)	Failure (%)	p value
≤30 days	Vancomycin	9 (36)	16 (64)	0.41
	Ampicillin	6 (40)	9 (60)	1
	Rifampin[a,b]	12 (60)	8 (40)	0.04
	Aminoglycoside[a]	3 (30)	7 (70)	0.49
	Linezolid	4 (80)	1 (20)	0.15
	Daptomycin	0	1	1
>30 days	Vancomycin	37 (65)	20 (35)	0.60
	Ampicillin	30 (67)	15 (33)	0.49
	Rifampin[a]	35 (58)	25 (42)	0.31
	Aminoglycoside[a]	20 (54)	17 (46)	0.20
	Linezolid	6 (46)	7 (54)	0.22
	Daptomycin	3 (43)	4 (57)	0.42

[a]In combination with one or more active antibiotics against enterococci.
[b]With vancomycin in six cases, with vancomycin and aminoglycoside in one case, with ampicillin and aminoglycoside in four cases, with linezolid in two cases and with other antibiotic in seven cases.

Discussion

To our knowledge, this is the largest case series of PJI due to *Enterococcus* sp. Prosthetic joint infections due to *Enterococcus* sp. were diagnosed within the first 2 years from arthroplasty in 79% of the cases and 48% of the patients had at least one comorbidity (diabetes mellitus, coronary disease, chronic renal failure, chronic obstructive pulmonary disease, malignancy or liver cirrhosis). This microorganism has been classically considered a difficult-to-treat pathogen, therefore, one-stage exchange is contraindicated and two-stage exchange is recommended [12]. The previous largest series by El Helou *et al.* [11] that reviewed the outcome of 50 enterococcal PJI found a 2-year cumulative probability of success of 94% for patients treated with two-stage exchange, 76% for those treated with resection arthroplasty, and 80% for patients treated with debridement and retention of the components, results comparable to those reported for other microorganisms [13]. However, they only included monomicrobial

infections and the first finding of our multi-centric study was that 54% of these infections were polymicrobial and they were associated with a higher failure rate than monomicrobial infections (52% versus 36%, p 0.042). Only late infections treated with implant removal had a remission rate of 92% (Table 2), similar to that described by El Helou *et al.* [11], but other infections treated with either debridement or removal of the implant had remission rates ≤50%. A potential explanation is that late infections (>2 years from arthroplasty) were less frequently polymicrobial than other infections (>2 years from arthroplasty; 32% versus 59%). More recently, Rasouli *et al.* [14] retrospectively reviewed 36 cases (39% polymicrobial). Irrigation and debridement were performed in 11 patients as the initial treatment; however, eight of these 11 patients needed reoperation to control the infection. These results are worse than those reported for *S. aureus* treated with debridement [15,16] or implant removal [13] and support the concept that the isolation of *Enterococcus* sp. is associated with bad results, especially in PJI due to *E. faecium* (Fig. 1).

It is difficult to know whether the poor results obtained in enterococcal PJI are due to the affected population having comorbidities, the high rate of polymicrobial infections, the severity of the infection, the ability of enterococci to form biofilms or the lack of potent antibiotics against enterococci [17,18]. Previous experience in a short case series of PJI due to different microorganisms showed that enterococci as well as methicillin-resistant *S. aureus* were independent predictors of failure [9], suggesting that particular virulence or the lack of effective antibiotics plays a role. Indeed, the analysis of the main antibiotics used in early infections showed that those patients receiving rifampin in combination with other active antibiotic (vancomycin, ampicillin, aminoglycoside or linezolid) had a higher remission rate than the alternatives without rifampin (60%, p 0.04); however, larger studies are necessary to confirm this finding. Linezolid also had a high remission rate (80%) but only five patients received this antibiotic and the difference was not statistically significant. Interestingly, linezolid–rifampin combination has a good effect on *E. faecalis* biofilms *in vitro* [19]. The administration of aminoglycosides was associated with a lower remission rate than other alternatives, similar to what El Helou *et al.* [11] described previously but in both cases there may be a selection bias because more severe infections are candidates to receive an aminoglycoside. *In vitro* and animal models have documented synergy between ampicillin and ceftriaxone [20] and recently, Euba *et al.* [21] described the efficacy of this combination in ten patients with orthopaedic infections with a remission rate of 90%; however, only three were PJI. Other potential combinations for the future could be a β-lactam plus daptomycin [22,23] or fosfomycin [24].

There is increased interest in one-stage exchange for PJI because it is associated with lower morbidity than two-stage exchange [25]. The case series published by Rasouli *et al.* [14] included six patients who underwent one-stage exchange and the components were still in place at the latest follow up, although one patient needed later irrigation and debridement. The number of patients was low and we cannot rule out a selection bias favouring one-stage exchange in the less severe PJI.

The main limitation of our study is its retrospective nature collecting information from different centres where the decision for surgical approach or antibiotic treatment relied on many different physicians. In addition, the number of variables evaluated was limited and other factors (e.g. obesity, previous surgeries, soft-tissue state) potentially influencing the outcome were not recorded. However, this is the largest case series from different countries and provides much information about the characteristics and outcome of enterococcal PJI.

In conclusion, PJI due to *Enterococcus* sp. were diagnosed within the first 2 years from arthroplasty in >70% of the cases, and almost 50% were associated with at least one comorbidity and were frequently polymicrobial infections (54%). The global failure rate was 44% and patients with comorbidities, fever and diagnosed within the first 2 years from arthroplasty had a poor prognosis.

Transparency Declaration

No funding was received. Alex Soriano has been speaker for Pfizer and Novartis. Eric Senneville has been speaker for Sanofi-Aventis and Novartis. Dolors Rodriguez-Pardo has been speaker for Pfizer, Novartis, Merk and Astellas. Rihard Trebse is consultant for Zimmer, J&J and CeramTec. Natividad Benito has been a consultant for MSD and Pfizer.

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